UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/315,292	05/20/1999	CLARENCE FRANK BENNETT	ISIS-3561	6344

32650 7590 11/15/2004

WOODCOCK WASHBURN LLP
ONE LIBERTY PLACE - 46TH FLOOR
PHILADELPHIA, PA 19103

EXAMINER	
BOWMAN, AMY HUDSON	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 11/15/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/315,292	BENNETT ET AL.	
	Examiner	Art Unit	
	Amy H Bowman	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 66-77 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 66-77 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to the communication filed 9/24/2004. Claims 1-65 have been cancelled. New claims 66-77 are pending in the instant application.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 66 and 76 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Regarding claim 66, it is unclear what sugar moiety is being referred to. There is no connection between "introducing the aerosolized oligonucleotide into the lung of the mammal" and "the sugar moiety of at least one nucleoside unit of the oligonucleotide is a 2'-O-substituted nucleoside unit." Applicant may wish to insert "wherein" between these two statements.

Claim 76 recites the limitation "said animal" of claim 66, although claim 66 does not recite an animal. Claim 66 recites "mammal". There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 66-77 are rejected under 35 U.S.C. 103(a) as being unpatentable over Debs et al. in view of Fulton et al., further in view of Tereshko et al.

The invention of claim 66 is drawn to a method for administering an oligonucleotide into a lung of a mammal comprising aerosolizing the oligonucleotide and introducing the aerosolized oligonucleotide into the lung of the mammal, further comprising at least one 2'-O-substituted nucleoside unit. Claims 67, 68, and 69 further limit the 2'-O-substituent to be a 2'-O-alkoxyalkoxy substituent, a 2'-O-methoxyethyl, and a 2'-O-dialkylaminooxyalkyl substituent, respectively. Claim 70 specifies that the methods of claims 66, 67, 68, or 69 wherein said oligonucleotide contains at least one phosphorothioate linkage. Claim 71 specifies that the oligonucleotide of the method of claim 66 contains at least one internucleotide linkage that is a 3'-methylenephosphonate, a non-phosphorous containing oligonucleoside linkage, a 2'-5' linkage or is a 3'-deoxy-3'-amino phosphoramide linkage. Claims 72-75 specify the method of claim 66 wherein the oligonucleotide is in an aqueous media, is in a sterilized, pyrogen free water, is in a saline solution, or is in a powder, respectively. Claim 76 specifies the method of claim 66 wherein the animal is known or suspected to suffer from a disease or disorder which may be treated or diagnosed by said oligonucleotide. Claim 77 specifies the disorder or disease to be asthma, a cancer of the lung, pulmonary fibrosis, rhinovirus, tuberculosis, bronchitis, or pneumonia.

Debs et al. (U.S. 6,468,798 and U.S. 5,858,784) teach methods for administration of antisense nucleic acids to the lungs of a mammal, wherein the aerosolized composition comprises liquid or solid particles or powder, a pharmaceutically acceptable carrier including sterile, pyrogen free water, or saline solution ('784- column 6, column 14-column 26, claim 11; '798- column 6, column 14-column 26, claims 1-33). Debs et al. ('784) teach the delivery of genes to the lung via aerosol administration, and subsequent expression in vivo (example 1) as a means for treating disorders of the lung (abstract). Debs et al. do not teach a 2'-O-substituent as specified in the instant claims.

Fulton et al. teach the ability to directly localize the administration of a compound by inhalation into the lungs (page 6, paragraph 1). Oligonucleotides are described to include antisense oligos and ribozymes, as well as other catalytic nucleic acid molecules including analogs and derivatives (page 30, paragraph 6). Various modifications to the DNA molecules are described as a means of increasing intracellular stability and half-life, including nucleotide sugar modifications such as 2'-O-modifications, as well as methyl phosphonate or phosphorothioate linkages (page 31, paragraphs 3 and 4).

Tereshko et al. teach 2'-O-modification of antisense oligonucleotides (page 10626, paragraph 1). Tereshko et al. teach advantages to using 2'-O-modified oligonucleotides, rather than unmodified oligonucleotides. Several advantages were identified for modifications such as 2'-O-methoxyethyl, such as increased nuclease resistance, increased stability of duplexes between modified strands and their RNA

complements, and overall enhanced RNA affinity (page 10626, paragraph 2; figure 1). Specifically, 2'-O-methoxyethyl substituents were shown to improve RNA affinity and improve pairing specificity compared with DNA (page 10632, Conclusions). Tereshko et al. do not teach the aerosolization of antisense oligonucleotides.

Debs et al. teach methods for the administration of antisense nucleic acids to the lungs of a mammal wherein the aerosolized composition comprises liquid or solid particles or powder, a pharmaceutically acceptable carrier including sterile, pyrogen free water, or saline solution. Although Debs et al. do not teach a 2'-O-substituent or phosphorothioate linkage, it would have been obvious to a person of ordinary skill in the art at the time the invention was made to use the method of Debs et al. in combination with the 2'-O-substituted oligonucleotides or phosphorothioate linkages of Fulton et al. with the motivation to gain the known benefits, which include increased nuclease resistance, intracellular stability, and half-life. Fulton et al. specifically discuss the ability to deliver antisense oligonucleotides with modifications, such as 2'-O-modifications or phosphorothioate linkages, to the lungs via inhalation. Additionally, Tereshko et al. teach 2'-O-modifications, such as 2'-O-methoxyethyl, to increase nuclease resistance and increase RNA affinity. One of ordinary skill in the art at the time the invention was made would conclude that 2'-O-modifications and phosphorothioate linkages are applicable to oligonucleotides being delivered to the lungs via inhalation and would enhance the effectiveness of the antisense oligonucleotides. There would have been a reasonable expectation of success to deliver 2'-O-substituted oligonucleotides or 2'-O-substituted oligonucleotides in combination with sugar-phosphate backbone

modifications via aerosolization due to the known success of delivering antisense oligonucleotides by aerosolization in a pharmaceutically acceptable carrier, as taught by Debs et al., and the known advantages of utilizing 2'-O-substituted oligonucleotides and sugar-phosphate backbone modifications, as taught by Fulton et al.

Therefore, the inventions of claims 66-75 would have been obvious, as a whole, at the time the instant invention was made.

Applicant's arguments with respect to claim 63 being improperly rejected under 35 U.S.C. 103(a) for being unpatentable over Debs et al. (U.S. 6,468,798) in view of Bennett et al. (U.S. 5,514,788) are considered to no longer apply since Bennett et al. is no longer relied upon.

Double Patenting Rejection

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 66-77 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 30, 32-35, 39, 40 and 43-46 of copending Application No. 09315581. Although the conflicting claims are not identical, they are not patentably distinct from each other because the scope of the claims encompasses the same invention.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The instant invention is drawn to a method for administering an oligonucleotide into a lung of a mammal comprising aerosolizing the oligonucleotide and introducing the aerosolized oligonucleotide into the lung of the mammal, further comprising at least one 2'-O-substituted nucleoside unit, as displayed in the above U.S.C. 103 rejection.

Patent Application '581, claims 30, 32-35, 39, 40 and 43-46, are broadly drawn to a method comprising aerosolizing a composition comprising at least one antisense oligonucleotide having SEQ ID NO:1,2,3,4,5,6,7,8,9,12,13,14, or 15 and introducing the aerosolized composition into the lung of a mammal (claim 30). Said composition is in aqueous media; sterilized, pyrogen free water; saline solution; or powder (claims 32-35). Said oligonucleotide comprises one or more phosphodiester linkages or one or more phosphorothioate linkages (claims 39 and 40). A method is claimed wherein the aerosolized composition is applied to the lung of an animal is known or suspected to suffer from a disease or disorder, wherein the disease or disorder is asthma, a cancer of the lung, pulmonary fibrosis, rhinovirus, tuberculosis, bronchitis, or pneumonia (claims 43-46). None of the claims specifically recite wherein the oligonucleotide has a 2'-O-

modification. However, the claims are broad and encompass such. See specification, page 19, wherein the usage of 2'-O-substituted nucleoside units is specifically discussed, as in instant claim 66. Therefore, the invention of '581 reads on 2'-O-modifications.

Although the invention being instantly claimed does not specify a particular antisense sequence or target gene, antisense sequences and target genes are disclosed on page 34 of the instant specification (SEQ ID NOS: 1,2,3,4,7, and 8) that are identical to the sequences and genes claimed in application '581 (SEQ ID NOS: 1,2,3,4,8, and 9). Thus, each of the instant application and '581 claim overlapping subject matter drawn to embodiments which are the same. Therefore, the instant claims and the claims of '581 are each obvious over the other in view of the overlapping scope.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amy H. Bowman whose telephone number is 571-272-0755. The examiner can normally be reached on Mon-Fri 7:30 am – 4:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance.

Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see http://pair-direct.uspto.gov.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Amy H. Bowman
Examiner
Art Unit 1635

JOHN L. LeGUYADER
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600